Mukandavire, C., Low, A., Mburu, G., Trickey, A., May, M., Davies, C., French, C., Looker, K., Rhodes, T., Platt, L., Guise, A., Hickman, M., & Vickerman, P. (2017). Impact of opioid substitution therapy on the HIV prevention benefit of antiretroviral therapy for people who inject drugs. *AIDS*, *31*(8), 1181–1190. https://doi.org/10.1097/QAD.0000000000001458

Title: Impact of opioid substitution therapy on the HIV prevention benefit of antiretroviral therapy for people who inject drugs

Short title: Impact of OST on ART for prevention

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Word count 3404

Abstract

Word count 250

Objective: A recent meta-analysis suggested that opioid substitution therapy (OST) increased uptake of anti-retroviral treatment (ART) and HIV viral suppression. We modelled whether OST could improve the HIV prevention benefit achieved by ART amongst people who inject drugs (PWID).

Methods: We modelled how introducing OST could improve the coverage of ART across a PWID population for different baseline ART coverage levels. Using existing data on how yearly HIV-transmission risk is related to HIV plasma viral load, changes in the level of viral suppression across the population were used to project the relative reduction in yearly HIV-transmission risk achieved by ART, with or without OST, compared to if there was no ART - defined here as the prevention effectiveness of ART.

Results: Due to OST use increasing the chance of being on ART and achieving viral suppression if on ART, the prevention effectiveness of ART for PWID on OST (compared to PWID not on OST) increases by 44%, 31% or 20% for a low (20%), moderate (40%) or high (60%) baseline ART coverage, respectively. Improvements in the population-level prevention effectiveness of ART are also achieved across all PWID, compared to if OST was not introduced. For instance, if OST is introduced at 40% coverage, the population-level prevention effectiveness of ART could increase by 27%, 20% or 13% for a low (20%), moderate (40%) or high (60%) baseline ART coverage, respectively.

Conclusions: OST could markedly improve the HIV prevention benefit of ART; supporting strategies that aim to concurrently scale-up OST with ART.

Keywords: antiretroviral therapy, opiate substitution therapy, HIV, viral suppression, injecting drug use, treatment as prevention

Introduction

Injecting drug use is an important driver of HIV transmission in Eastern Europe, North America, and parts of Asia[1, 2], and is increasing in many settings including East Africa[3-5].

While the use of antiretroviral treatment (ART) has improved the lives of those infected with HIV[6-10] and can dramatically reduce HIV transmission (by 96% amongst sero-discordant couples[11]), access to treatment and treatment outcomes are frequently inferior amongst PWID due to a range of factors[12-14]. This could hinder the worldwide goal of achieving high coverage of HIV treatment and viral suppression for dramatically reducing global levels of HIV transmission and morbidity[15].

Existing evidence suggests opioid substitution therapy (OST) can reduce the frequency of injecting drug use[16, 17], halve the risk of HIV and HCV acquisition among PWID[18, 19], and reduce drug-related mortality[20]. Evidence is also emerging that concurrent OST use can improve ART outcomes amongst PWID, including the uptake and retention on ART, and the level of treatment adherence and viral suppression, as synthesised in a recent meta-analysis[21].

We used data from this meta-analysis to estimate the degree to which OST could increase the HIV prevention benefit of ART amongst PWID. We first compared the average HIV prevention protection achieved by ART amongst PWID on OST to PWID off OST, and then compared the average prevention protection achieved by ART at the population-level with and without the introduction of OST. These population-level projections either assumed no change in ART coverage amongst PWID not on OST, or alternatively evaluated how the dynamic nature of PWID coming on and off OST could increase the coverage of ART amongst PWID off OST.

Methods

Definition of ART prevention effectiveness

We evaluate the HIV prevention protection provided by ART for a specific PWID sub-population by estimating the degree to which the level of ART use in that sub-population decreases the annual HIV transmission risk averaged across all HIV-infected PWID on and off ART. We denote this the **prevention effectiveness** of ART for that sub-population, which depends both on the coverage of ART amongst HIV-infected PWID in that sub-population and the degree to which ART decreases the yearly HIV transmission risk or infectivity of those PWID on ART, as determined by their decrease in viral load after initiating ART[22].

Static estimation of benefits of OST

Assuming a certain coverage of ART amongst those not on OST, and level of viral suppression amongst those on ART, synthesised effect estimates from our meta-analysis[21] were used to estimate the increased ART coverage amongst those currently on OST and increased proportion virally suppressed amongst those on OST and ART. This did not utilise synthesised estimates for the effect of OST on ART recruitment or retention[21], but just estimates for its effect on increasing ART coverage amongst those on OST, with no change in ART coverage amongst those off OST. For those on ART that are virally suppressed or unsuppressed, estimates of their log difference in viral load compared to PWID not on ART were used to estimate the relative decrease in HIV infectivity achieved through ART. These calculations utilised an existing observed association between plasma viral load (PVL) and yearly HIV transmission risk in sero-discordant couples[22]. For different ART and OST intervention coverage combinations, estimates of the relative decrease in HIV infectivity were then averaged across the proportion virally suppressed or not for specific sub-groups to produce and compare estimates of the prevention effectiveness of ART. We estimated the relative increase in the prevention effectiveness of ART for PWID on OST compared to PWID off OST, and at the population-level for different OST coverage levels compared to if OST had not been introduced. See supplementary materials for more methodological details.

Dynamic estimation of benefits of OST

A dynamic model of OST and ART recruitment and retention amongst HIV-infected PWID was developed. The model assumed PWID on OST have improved ART recruitment and retention. Through PWID transitioning on and off OST, this allowed improvements in ART uptake amongst PWID on OST to effect ART coverage levels amongst PWID not on OST. This contrasts with the static model, which assumed a heightened ART coverage only amongst PWID on OST. The dynamic model was used to re-estimate the increase in ART coverage that could occur at the population-level due to introducing OST, and the population-level prevention effectiveness of ART for different OST coverage levels compared to if OST had not been introduced.

The dynamic model stratifies HIV-infected PWID by ART (never, currently or previously on ART) and OST (not on OST, short- or long-term OST) status. HIV-positive PWID join the model at a constant rate calibrated to give a population of 1,000,000 HIV-positive PWID before ART is scaled-up. We do not consider any dynamic effect of ART on the rate of new HIV-positive PWID because we are only interested in the short-term benefits of OST on ART outcomes. PWID leave the model due to non-HIV

death or injecting cessation. ART-naïve HIV-infected PWID also experience HIV-related mortality, or can be recruited onto ART. When on ART, HIV-related mortality is reduced, but PWID can discontinue HIV treatment. PWID discontinuing ART can recruit back on to ART, but at a lower rate than ART-naïve PWID. Recruitment onto OST occurs independently of ART status. When initiated on to OST, PWID enter short-term OST, from which they either leave OST or transition to long-term OST. PWID generally leave long-term OST at a reduced rate. When on OST, recruitment onto ART is increased and attrition is reduced[21]. The schematic for the dynamic model is shown in Figure 1 and parameters defined in Table 1, with model equations given in the supplementary materials.

Model parameterisation

The models were parameterized using data from various sources (Table 1). Firstly, the meta-analysis[21] gave estimates for how being on OST improved the coverage of ART (static model), the rates of recruitment onto and retention on ART (dynamic model), and the proportion on ART that are virally suppressed (both models). The estimated baseline PVL amongst PWID off ART was obtained from the Antiretroviral Therapy Cohort Collaboration study[23] carried out among 5761 PWID in Europe and North America who initiated ART between 1996 and 2013. The same study gave estimates for the proportion of PWID not virally suppressed at 12 months after initiating ART, and the decrease in PVL from baseline for virally suppressed and unsuppressed PWID.

The dynamic model required additional data to parameterise the dynamics of OST and ART retention and mortality (Table 1). A wide range was used for the combined rate of injecting cessation and non-HIV mortality (5-25% per year) because of uncertainty across settings[20, 24-26]. HIV-related mortality[27, 28] was assumed to reduce by 66-80% if on ART[29-33]. Estimates for the baseline level of ART retention amongst PWID were derived from a pan-European study[34], whereas ART recruitment rates were calibrated to give different baseline ART coverage levels.

Data for long-term attrition from OST are limited[35]. To model long-term attrition from OST, we combined five international datasets which captured OST retention for over a year ([36-39] and Hickman unpublished). These data were used to give a range for the long-term retention of PWID on OST (Figure S2 and S3), which were sampled for subsequent model runs (supplementary materials for details). Uniform distribution ranges for each parameter are given in Table 1. Lastly, OST recruitment rates were calibrated to give different OST coverage scenarios.

Model analyses – Static model

To incorporate uncertainty, 1000 parameter sets were randomly sampled from the static model parameter distributions given in Table 1. For each sampled parameter set, and a wide range of baseline ART coverage levels (10-90% when no OST), we estimated the absolute and relative increase in the prevention effectiveness of ART for PWID on OST compared to PWID not on OST. For different OST coverage levels (20, 40, 60 and 80%), we then estimated how the population-level prevention effectiveness of ART increases compared to if OST was not introduced.

Model analyses – Dynamic model

For the dynamic model, all additional model parameters with uncertainty distributions in Table 1 were randomly sampled to give 1000 parameter sets. For each parameter set, the ART recruitment rate was firstly calibrated to give a range of steady baseline ART coverage scenarios (10-90%). Then, for each ART scenario, OST was introduced with different OST recruitment rates being used to give a range of steady OST coverage levels (20, 40, 60, and 80%).

For each OST and ART coverage scenario, we projected the degree to which OST increased the overall coverage of ART, and ART coverage among PWID on OST compared to PWID off OST. The ART coverage estimates for PWID on and off OST were then combined with the sampled parameter sets for the static model (other than ART coverage parameters) to re-estimate the degree to which OST increases the population-level prevention effectiveness of ART for different OST and ART coverage levels.

Uncertainty analysis

A linear regression analysis of covariance (ANCOVA)[40] was undertaken to determine which parameter uncertainties contribute most to variability in the dynamic model's projections. We considered the relative increase in the population-level prevention effectiveness of ART for the scenario where the coverage of OST and baseline ART coverage were 40%. The proportion of the model outcome's sum-of-squares contributed by each parameter was calculated to estimate the importance of individual parameters to the overall uncertainty.

Results

Static model projections

The static model suggests that being on OST (compared to not) could increase the absolute prevention

effectiveness of ART by a median of 6.5 (2.5th to 97.5th percentile range: 2.8-11.8), 9.4 (4.2-15.5) or 9.3 (4.3-14.4%) percentage points, for a baseline ART coverage of 20, 40 or 60%, respectively (Figure 2(a)). For instance, for a baseline ART coverage of 40%, being on OST improves the average prevention effectiveness of ART from 31.8% (19.1-37.4%) to 40.7% (27.0-51.0%). These absolute changes translate to relative improvements in ART prevention effectiveness of 43.8% (17.0-78.8%), 31.0% (12.7-56.6%) and 19.9% (8.6-39.9%) for baseline ART coverages of 20, 40 or 60%, respectively (Figure 2(b)). Most (generally >80%) of this improvement in prevention effectiveness of ART is due to the increase in ART coverage amongst those on OST (compared to those off OST) instead of their improvement in viral suppression (Figure S4).

If OST only improves the coverage of ART amongst those on OST, as assumed by the static model, then a high OST coverage (60%) could improve the population-level prevention effectiveness of ART by 26.3% (10.2-47.3%), 18.6% (7.6-34.0%) and 11.9% (5.2-23.9%) for a baseline ART coverage of 20, 40 and 60%, respectively (Figure 3(a)). If OST coverage is 40% instead of 60%, then this reduces to 17.5% (6.8-31.5%), 12.4% (5.1-22.6%) and 8.0% (3.5-15.9%) for the same baseline ART coverage levels. Although less relative benefit is achieved by OST at higher ART coverage levels, the absolute effects are similar as presented in the previous paragraph.

Dynamic model projections

In contrast to the static model, the dynamic model incorporates PWID transitioning on and off OST. Through including this effect, the dynamic model projects a greater (Figure 4) increase in ART coverage due to OST. For a 20, 40 or 60% baseline ART coverage and OST coverage of 40%, the static model predicts a 15.0% (5.6-26.6%), 10.3% (4.1-17.2%), 6.3% (2.6-10.0%) relative increase in ART coverage from baseline levels, whereas the dynamic model predicts a 25.2% (15.0-35.6%) , 17.8% (10.9-24.2%) and 10.9% (7.1-14.7%) relative increase. This means that for a baseline ART coverage of 40%, the static model predicts ART coverage would increase to 44.1% (41.6-46.9%) following OST scale-up to 40% coverage, whereas the dynamic model predicts ART coverage would increase to 47.1% (44.4-49.7%).

Subsequently, the dynamic model also predicts that OST scale-up will result in greater increases in the population-level prevention effectiveness of ART (Figure 3(b)) than the static model. For instance, the dynamic model projects that scaling-up OST to 40% coverage results in the population-level prevention effectiveness of ART increasing by 27.1% (16.2-39.6%), 19.7% (12.2-28.7%) or 12.6% (8.1-19.6%) for a baseline ART coverage of 20, 40 and 60%, respectively (Figure 3(b) and Table S1). This is about 60% more than was projected by the static model (figure 3(a)).

Uncertainty analysis

ANCOVA analyses (Figure S5) suggest that most variability in the dynamic model's projections of the relative increase in population-level prevention effectiveness of ART due to OST is due to uncertainty in the increased ART recruitment rate amongst PWID on OST compared to PWID off OST (accounts for 74.7% of variability). Additional variability is due to uncertainty in the log decrease in viral load among unsuppressed PWID on ART compared to PWID not on ART (15.0%), the proportion virally suppressed for PWID on ART but not OST (2.3%), and the decreased ART attrition rate amongst PWID on OST compared to PWID off OST (2.5%).

Discussion

Our findings suggest that OST could markedly increase the HIV prevention benefit of ART for PWID. At the population-level, moderate OST coverage (40%) could increase the prevention effectiveness of ART by about a quarter if the baseline ART coverage is low to moderate (20-40%) or about half of this if ART coverage is high (60%). This beneficial effect largely results from OST increasing the coverage of ART amongst those on OST, and as a by-product increasing the coverage of ART amongst those not on OST through PWID transitioning on and off OST. However, if OST scale-up does not increase ART coverage amongst PWID not on OST, then the degree to which OST improves the population-level prevention benefit of ART is halved, but is still important for low ART coverage levels (<40%) or at the individual-level for all PWID on OST. It is likely that these indirect benefits of OST in improving the prevention benefit of ART could result in important gains in HIV infections averted (see supplementary materials); possibly comparable to the benefits achieved by OST through directly reducing injection-related HIV transmission risk.

Limitations

There are limitations to our projections. Firstly, there was uncertainty around many model parameters, such as the effect of OST on ART recruitment and coverage. Our modelling results were generally robust to these uncertainties, with only uncertainty in the factor increase in ART recruitment for PWID on OST compared to PWID off OST resulting in sizeable uncertainty in our projections. Improved data on this parameter is needed.

Other simplifying assumptions include the rate of non-HIV death and/or injecting cessation being the same for PWID on and off OST. Studies generally show that OST improves drug-related mortality[20] and may increase injecting cessation[41, 42]. Although important effects, it is unlikely that they will affect our results, as suggested by our uncertainty analysis and previous analyses[43]. Additionally,

the dynamic model assumed that OST and ART attrition occurred independently of each other, which resulted in the model projecting that OST scale-up could also increase ART coverage amongst PWID not on OST. However, although data is sparse, it is possible that both events could be linked, with ART attrition being more likely when PWID cease OST. This could be due to both treatments being dispensed alongside each other, or a common structural factor or event hindering further use of both services, such as incarceration. If this were the case in specific settings, then the results of our static model could be closer to reality. For determining which model is most valid in a specific setting, it is important to understand the different reasons for PWID leaving OST and ART, and so the likelihood of the events being linked. Insights into this could also be aided by observing the degree to which OST and ART attrition at the individual-level occurs over similar follow-up periods in observational studies of PWID on OST and ART [21].

There is also uncertainty around the efficacy of ART for reducing injecting HIV transmission. Although it is likely that ART will reduce the risk of injection-related HIV transmission, due to large reductions in viral load, the actual efficacy is uncertain[44]. While this would affect our estimates of the prevention benefit of ART, it should not affect the relative degree to which OST improves the prevention effectiveness of ART, as suggested by our uncertainty analysis. Additionally, although limited data suggests parenteral HIV transmission risk may increase with heightened viral load[45], no data exists on the precise relationship. Our analyses therefore relied on data from sero-discordant couple studies suggesting that heterosexual HIV transmission risk is strongly related to the logarithm of the plasma viral load[22]. However, other analyses have suggested alternative relationships, with Fraser et al. proposing a saturating effect at high viral loads[46], but reassuringly our results are robust to this different assumption (see supplementary materials). Moreover, although HIV transmission risk amongst PWID is likely to depend on more complex behavioural and network factors than amongst sero-discordant couples, it should still be reasonable to assume that ART will similarly effect levels of HIV transmission risk as considered in this analysis.

The model used in this analysis only considered the short-term benefits of OST in increasing the impact of ART on yearly HIV transmission risk. Over time, any differences in transmission risk between two intervention scenarios could be amplified due to heightened reductions in HIV prevalence in the ART with OST scenario, and so our projections may be conservative. Conversely, the model assumed all HIV-infected PWID are equally likely to be on ART, and so did not account for the initial phase of HIV infection when individuals are unlikely to be on ART but will have elevated HIV infectivity[47]. Although this may reduce the prevention effectiveness of ART, it should have less

effect on the degree to which OST improves the benefits achieved. The analysis also did not consider the direct prevention benefit of OST scale-up on HIV transmission, and so underestimates the overall benefits achieved from scaling-up OST. Future modelling should consider the longer-term combined benefits of scaling up OST and ART, while incorporating the synergies between these interventions.

Lastly, the projections of this model were primarily based on findings from a recent meta-analysis that synthesised evidence on the effects of OST use on different ART outcomes[21]. Although this should be considered a strength of the model analysis, weaknesses in the synthesised datasets, including the reliance on observational cohorts does raise concerns which could only be reduced through further data collection. However, future studies will still likely rely on observational cohorts, with their inherent weaknesses, because the other proven benefits of OST[18, 20, 48, 49] restrict the ability to randomise PWID onto OST or not. Other weaknesses of the synthesised studies include little in-depth consideration of the reasons why PWID did not achieve optimal ART outcomes, including viral suppression, and the likely reasons why OST improved these outcomes. Instead, current studies generally have just evaluated the overall effect of OST on improving different ART outcomes, and our model made the same simplifying assumption. It is important that future studies seek to understand the processes by which OST achieves a beneficial effect, and determine whether OST only acts on certain factors impeding optimal ART outcomes. This would benefit future intervention design as well as modelling to evaluate the benefits of OST for improving ART outcomes amongst PWID.

Comparison with other studies

A recent systematic review found that OST can halve the risk of HIV acquisition among PWID[18], and numerous modelling analyses have suggested that scaling up OST and/or ART amongst PWID could dramatically reduce HIV transmission[50-52], and be cost-effective[53-55]. This is the first study to demonstrate that OST could improve the prevention benefits of ART.

Implications and Conclusions

Accumulating evidence suggests that OST could dramatically improve the cascade-of-care amongst HIV-infected PWID[21, 33, 56], with modelling in this paper further suggesting that these improvements could enhance the effectiveness of ART in reducing HIV transmission. These findings add to the evidence base for the multiple benefits of OST[57-60], and support strategies to integrate OST with HIV services to optimise the benefits achieved. Unfortunately, many countries have low OST coverage, or even forbid its provision[61, 62], and PWID frequently have sub-optimal coverage

of ART[29]. Many of these countries have significant on-going HIV epidemics or have experienced new HIV outbreaks[4, 63-69]. In these settings, the joint scale-up of OST with ART could have a substantial effect on HIV transmission and morbidity, and is likely to be highly cost-effective[70-72]. However, to optimise the impact of OST a number of structural and policy barriers will have to be overcome to increase the uptake of OST and/or ART among PWID, including reducing the stigmatisation of PWID in health settings and reducing the criminalisation of drug use[73].

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Funding

This work was supported by the International HIV/AIDS Alliance [AIDS Alliance 711]. This work was additionally supported by the National Institute for Drug Abuse [grant number R01 DA037773-01A1] to PV and MH; National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Evaluation of Interventions at University of Bristol to PV, CF, KT, KL, HC and MH; National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in STI & BBV at University College London to PV; UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement and the EDCTP2 programme supported by the European Union to MM; and Bill and Melinda Gates Foundation HIV modelling consortium to PV. The views expressed are those of the author(s) and not necessarily those of the University of Bristol, UK NHS, the UK NIHR or the UK Department of Health.

Contributions

PV and GM conceived of the study. PV and CM provided overall leadership for the study design, analysis and interpretation of the findings. CM developed the model and performed all model analyses. AT and MM undertook additional analyses of the Antiretroviral Therapy Cohort Collaboration study dataset. CM wrote the first draft of the manuscript with PV. All authors have contributed to the overall collaboration through guiding the initial analysis plan, interpreting the results, and writing subsequent versions of the manuscript.

Tables

Table 1. Parameter values and ranges used in models.

Variable or parameter	Symbol	Value (range used)	Source and comments
Parameters for static model			
ART coverage at baseline without effect of OST	x	0 - 100%	Varied for different ART scenarios
OST coverage	y	0 - 100%	Varied for different OST scenarios
Odds ratio for OST use increasing ART coverage (used in static model only)	r_a	1.54 (95%CI: 1.17-2.03)	[21]
Odds ratio for OST use increasing viral suppression on ART	r_s	1.45 (95%CI: 1.21-1.73)	[21]
Baseline plasma viral load when not on ART	v_b	4.79 (IQR: 4.11-5.27) log 10 copies/ml	[12, 23]
Plasma viral load among virally suppressed PWID on ART	v_s	1.7 log 10 copies/ml	Assume 50 copies/mL as limit of detection – translates to 92% decrease in HIV infectivity similar to trial[11]
Log difference in plasma viral load among unsuppressed PWID on ART compared to before they initiated ART	Δ_u	-0.81 (IQR: -2.27-0.00) log 10 copies/ml	Median (25 and 75% IQR) difference in plasma viral load 1 year after initiating ART compared to before ART[12, 23]
Factor difference in HIV transmission risk for each log increment in plasma viral load	r_t	2.45 (95%CI: 1.85-3.26)	[22]
Proportion virally suppressed among PWID on ART if not on OST	p_s	0.56 (0.35-0.86)	Median (2.5-97.5% range) for 9 studies from systematic review [21]
Additional parameters for dynamic model			
Baseline recruitment, mortality and cessation			
Constant yearly recruitment rate of PWID into HIV-positive population	Θ	(1.49-3.67)x10^5	Calibrated to give constant of population of 1000000 PWID before ART introduced
HIV mortality rate in the latent stage of HIV per year	δ	1/10.5-1/8.5	[27, 28]
Injecting cessation and non-HIV death rate per year	ν	5-25%	[42, 74-76]
OST parameters			
Recruitment rate onto OST per year	ε	To fit: 0-100%	Varied to fit different OST coverage scenarios
Rate of leaving short stay OST per year	κ	0.2-1.6	Estimated through fitting a split exponential function to OST retention data – see supplementary materials
Rate of leaving long stay OST per year	π	0.083-0.87	
Rate of moving from short to long stay OST per year	a	0.25-1.48	
ART parameters			
Baseline recruitment rate onto ART when not on OST per year	ω	To fit: 0-100%	Varied to fit different ART coverage scenarios
Cofactor difference in ART recruitment rate after having discontinued ART compared to when initiating ART	χ	0.5 - 1.0	No data so sampled in range
Cofactor difference in HIV mortality rate while on ART compared to latent stage	φ	1/5-1/3	[31-33]
Rate at which PWID on ART discontinue treatment per year	σ	2.99-9.84%	Estimated using data from [34] - see methods and supplementary materials
Effect of OST on ART outcomes			
Odds ratio for OST use increasing the rate of ART recruitment	b	1.87 (95%CI: 1.50-2.33)	[21]
Odds ratio for OST use decreasing the rate of ART attrition	d	0.77 (95%CI: 0.63-0.95)	[21]

Figures

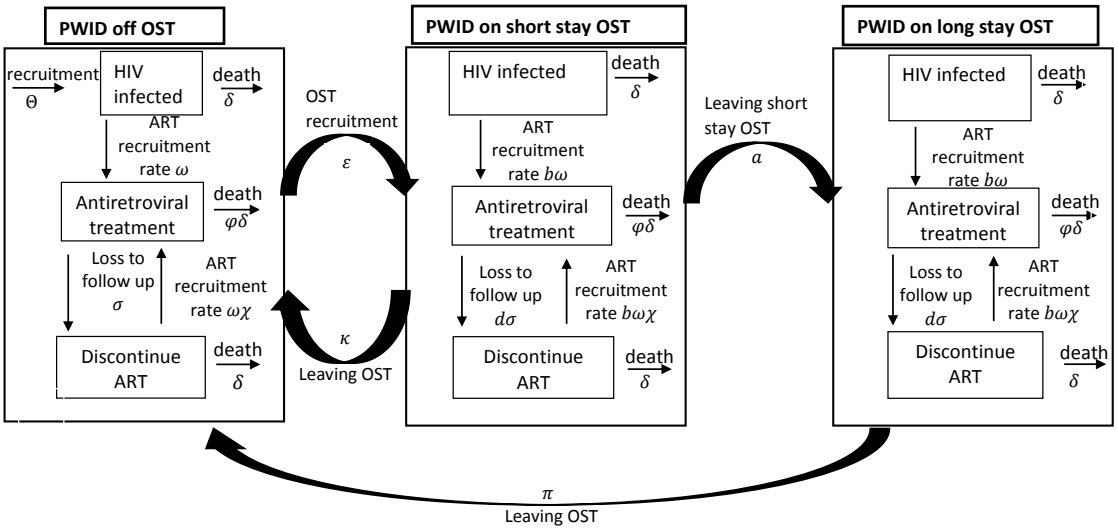
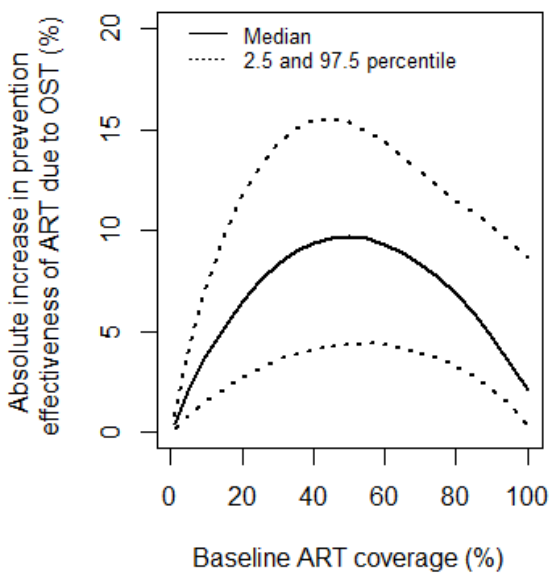
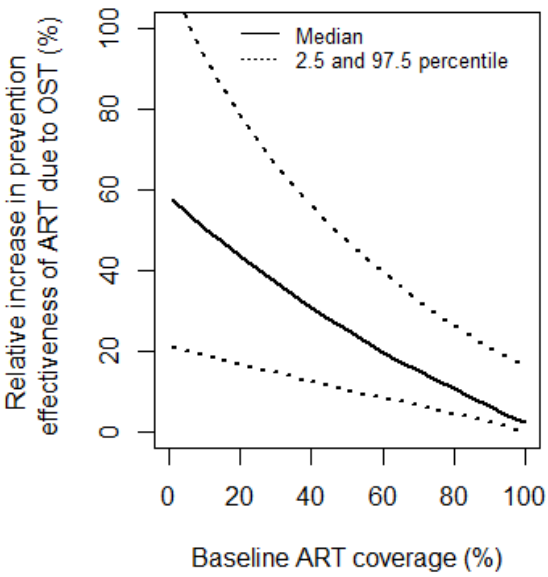


Figure 1. Model schematic showing dynamics of ART and OST recruitment and attrition amongst a population of HIV-infected PWID. Arrows show possible transitions from one state to the other and are labelled by the flow rates. New PWID enter the model in the HIV infected off OST compartment at a constant rate Θ and leave all compartments due to non-HIV death and injecting cessation at a rate ν. Modelled PWID not on anti-retroviral treatment (ART) also experience HIV-related death at a rate δ, and are recruited onto ART at a rate ω if not on OST and $b\omega$ if on OST. PWID on ART discontinue treatment at a rate σ if not on OST, and at a decreased rate $d\sigma$ if on OST. Those who discontinue ART can be recruited back onto ART at a rate $\omega\chi$. PWID are recruited onto OST at a rate ε and either have a short stay on OST for an average duration of $1/\kappa$ or move into the OST class for a long stay at a rate a. PWID remain in the long stay OST for an average duration of $1/\pi$.

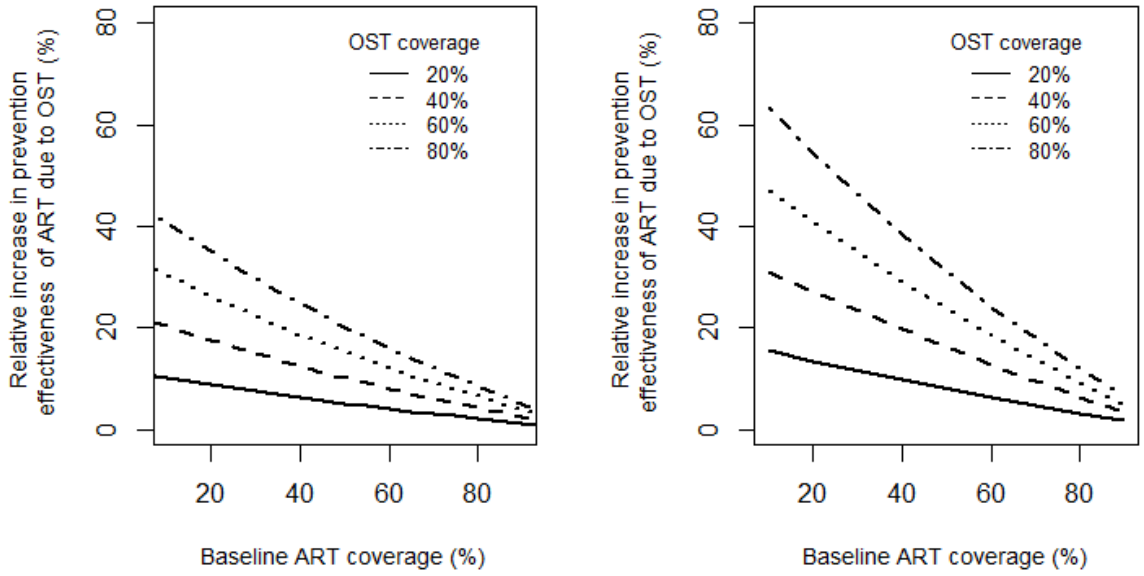


(2a) Absolute increase



(2b) Relative increase

Figure 2. Absolute (2a) and relative (2b) increase in the prevention effectiveness of ART for PWID on OST compared to PWID off OST. These projections hold irrespective of the level of OST coverage. Bold line shows the median and dotted lines show the 2.5th and 97.5th percentiles from 1000 sampled parameter sets.



(a) Static model projections (b) Dynamic model projections

Figure 3. Static (3a) and dynamic (3b) model projections of the relative increase in the population-level prevention effectiveness of ART for different OST coverages and baseline ART coverages (ART coverage before OST introduced), compared to before OST was introduced. The graph shows the median plots from the 1000 sampled parameter sets.

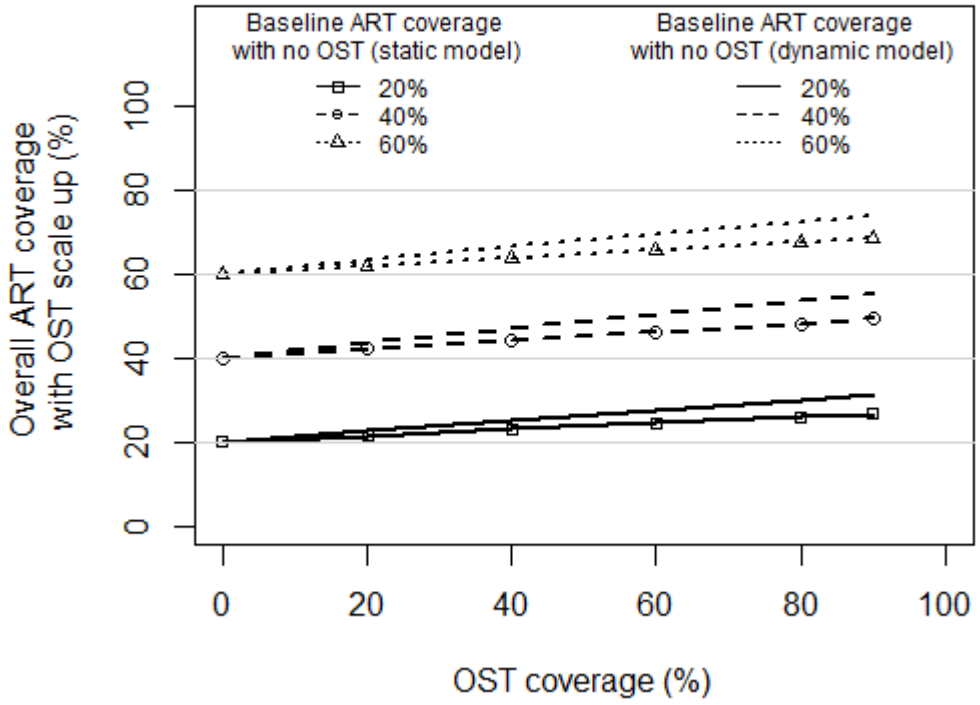


Figure 4. Overall increase in ART coverage as OST coverage increases for the static and dynamic models for baseline ART coverage levels of 20, 40 and 60%.